Risk factors and a clinical index for diagnosis of *Pseudomonas aeruginosa* bacteremia

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Objective: To define risk factors significantly and independently associated with *Pseudomonas aeruginosa* bacteremia and to combine them in a diagnostic index which will define groups of septic patients at low or high risk of bloodstream infection caused by *P. aeruginosa.*

Methods: Logistic regression analysis was used to identify risk factors associated with pseudomonal bacteremia among all patients with bacteremia at St Thomas' Hospital, London, from 1969 to1989. The coefficients of the final logistic model were used to compile a linear model for the diagnosis of pseudomonal bacteremia. The index was validated in another set of patients with bacteremia detected at Beilinson Medical Center, Petah Tiqva, Israel, from 1988 to 1991.

Results: Seven factors were significantly and independently predictive of pseudomonal bacteremia:1) neutropenia; 2) previous or current treatment with antibiotics; 3) cytotoxic or corticosteroid treatment; 4) hospital acquisition of infection; 5) detection in the intensive care unit; 6) male gender; and 7) focus of infection. High-risk foci were the urinary tract with catheter or post-instrumentation, or unknown source. Low-risk foci were bone, joint, meninges, female genital tract and upper respiratory tract. The index score divided patients into three groups with increasing likelihood of *P. aeruginosa* bacteremia: 1%, 7% and 19%, respectively ($p = 0.0001$). In the validation set, the percentage of *P. aeruginosa* bacteremia in the three respective groups defined by the index were 5%, 18% and 22% ($p = 0.0001$).

Conclusions: The use of simple clinical and laboratory data known within hours of detection of an infectious episode can define patients at high and low risk for *P. aeruginosa* bacteremia.

Key words: *Pseudomonas*, bacteremia, predictor

Pseudomonas aeruginosa accounts for 8 to 15% of hospital-acquired and 1 to 7% of community-acquired bacteremias [1-5]. The mortality associated with pseudomonal bloodstream infection is generally higher than with other pathogens even when different risk factors for mortality are taken into account [3,5,6]. Empirical therapy with appropriate antipseudomonal agents may reduce mortality [7-9], but it is likely to be inappropriate in patients subsequently shown to have *P. aeruginosa* bacteremia than in those with other bacterial pathogens [10]. Thus, prediction of the likelihood of a pseudomonal infection in a septic patient as early as possible (before the results of blood cultures are known) may be of utmost importance and would allow empirical treatment of patients at high risk for bacteremia caused by *P. aeruginosa* to include anti-pseudomonal drugs whereas patients at low risk could receive narrower-spectrum therapy.

The aim of the present study was to define the risk factors significantly and independently associated with *P. aeruginosa* bacteremia and to combine them in an index for prediction of the likelihood of pseudomonal bloodstream infection. For derivation of the risk factors and the index, we used the St Thomas' Hospital bacteremia database [11]. To show that the risk factors and index were general features of pseudomonal bacteremia and not related to one particular geographical site, they were validated in another hospital in a different country.

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METHODS

Population

The derivation set included all patients with bacteremia seen at St Thomas' Hospital, London, between 1969 and 1989. The hospital is an 800-bed teaching hospital in southeast London which serves the local population, commuters and some tertiary referrals. During the period of study, there were no specialist departments for cancer chemotherapy or burn patients.

The validation set consisted of all episodes of bacteremia detected at Beilinson Medical Center, Petah Tiqva, Israel, from March 1988 to September 1992. The Medical Center is a 900-bed hospital serving an urban population as a first-line facility. It is also a referral centre for several hospitals in the vicinity. To determine the possible influence of changing patterns of bacteremia over time, a second validation set was used, consisting of those episodes of bacteremia detected at St Thomas' Hospital from 1990 to 1993.

Collection of data

In both hospitals, collection of clinical and laboratory data was performed by medical microbiologists or physicians, and started on the day the first blood culture was found to be positive for bacterial growth. For each patient, demographic information, data concerning underlying diseases, functional capacity and medications were collected. For every episode of bacteremia, the presumptive source, the day and ward of occurrence, the use of intraurethral, intravascular or intratracheal devices, fever and results of the blood count and blood chemistry were recorded. During follow-up, data were collected on the antibiotic treatment, results of blood and other cultures, complications of bacteremia, and duration of hospitalization and outcome (whether discharge or death) [4,5,10].

Blood cultures

Venous blood (10 mL) was obtained aseptically and inoculated into a two-bottle set (6A aerobic and 7A anaerobic, Becton Dickinson Diagnostic Instrument Systems, Towson, MD, USA at St Thomas' Hospital; and 6B aerobic and 7D anaerobic, Johnston, Towson, MD at Beilinson Medical Center), and was tested daily on a Bactec 460 system at Beilinson and on a Bactec 660 at St Thomas' Hospital.

Definitions

For this study, bacteremia was defined as an episode in a patient judged to be 'septic' (febrile $\geq 38°C$ or hypothermic $<36.2°C$, hypotensive or in septic shock, with rigors or a 'septic appearance') and with positive (and not contaminated) blood cultures. Organisms that are commonly recovered from the environment or the skin (mainly coagulase-negative staphylococci and aerobic gram-positive rods) were judged to be contaminants unless the clinical findings, the results of cultures from other body sites or the number of positive sets ($\geq$ two) indicated a high probability of true bloodstream infection.

At St Thomas' Hospital, a bacteremic episode was defined as hospital-acquired if the infectious episode to which it was related began at any time after admission. At Beilinson Medical Center, a bacteremia was defined as hospital-acquired if it occurred more than 48 h after admission.

An episode of bacteremia was designated as antedated by antibiotic, corticosteroid or cytotoxic treatment if the drug(s) had been given for more than 1 day during the preceding month, and by an invasive procedure if performed within the preceding month. Empirical antipseudomonal antibiotic treatment was considered appropriate if it was started intravenously within 24 h of collection of the first positive blood culture, if it included antipseudomonal β-lactams, an aminoglycoside or one of the drugs that can be used as monotherapy for *P. aeruginosa* (ceftazidime, imipenem or a 4-quinolone), and if the isolate was subsequently found to be susceptible in vitro to the drug(s) administered.

Data analysis

Episodes of bacteremia caused by *P. aeruginosa* were compared with episodes caused by other pathogens. The chi-square test was used for statistical analysis of contingency tables. As most of the continuous variables were not normally distributed, the Wilcoxon rank-sum test was used to assess significance of continuous variables compared between two classes. A stepwise logistic regression procedure (LOGIST) [12] was used to establish which variables were independently and significantly associated with bacteremia caused by *P. aeruginosa*. The coefficients of the final logistic model were used to compile a linear model for diagnosis of *Pseudomonas* bacteremia.

RESULTS

Derivation set

At St Thomas' Hospital, there were 4447 episodes of clinically significant bacteremia during the period of study. *Pseudomonas aeruginosa* was the causative organism in 231 (5.2%). The mortality rate was 46.7% (108 of 231) in patients with *Pseudomonas* bacteremia, and 21.0% (885 of 4216) in patients with other pathogens ($p = 0.0001$). Comparisons which were statistically significant on univariate analysis ($p < 0.1$)

Table 1 Derivation set: Univariate comparisons of *Pseudomonas aeruginosa* bacteremia vs bacteremias caused by other pathogens at St Thomas' Hospital, London

	Pseudomonas aeruginosa % (n = 231)	Other pathogens % (n = 4216)	p
Age > 20 years	93.9	87.6	0.02
Male gender	68.0	54.6	0.0001
Service			
Intensive care unit	23.4	9.5	0.0001
Urology	13.4	7.3	0.03
Neutrophil count ≤ 1 × 10^9 cells/L	20.4	4.9	0.0001
Hospital-acquired	91.8	55.0	0.0001
Previous/current antibiotic treatment	61.9	26.1	0.0001
Focus of infection:			
High risk			
Urinary tract with catheter or post-instrumentation	16.5	8.3	0.001
Unknown	25.1	12.1	0.0002
Low risk			
Bone/joint	0.0	2.9	0.009
Meninges	0.4	3.3	0.02
Female genital tract	0.0	2.7	0.02
Upper respiratory tract	0.0	0.8	0.2
Underlying diseases			
Hematological malignancies	20.8	7.1	0.0002
Cytotoxic or corticosteroid treatment	33.3	14.0	0.0002

Table 2 Derivation set: Factors included in the final logistic model as predictors of pseudomonal bacteremia

Risk factor	Regression coefficient	χ^2	p	Points for score index
Previous/current antibiotic treatment	0.969	40.3	0.0001	1
Neutrophil count ≤ 1 × 10^9 cells/L	1.038	20.1	0.0001	1
Hospital-acquired	1.211	22.1	0.0001	1
Intensive care unit patient	0.804	18.9	0.0001	1
High-risk focus[a]	0.487	9.9	0.0001	0.5
Male gender	0.311	6.2	0.0013	0.5
Corticosteroid or cytotoxic treatment	0.623	10.9	0.0001	0.5
Low risk focus[b]	−2.089	28.4	0.004	−2

a = high-risk focus: urinary tract with catheter or post-instrumentation, or unknown;

b = low-risk focus: bone, joint, meninges, female genital tract and upper respiratory tract.

are shown in Table 1. On multivariate logistic regression analysis, seven factors were associated both significantly and independently with bacteremia caused by *P. aeruginosa*: 1) antibiotic treatment in the previous month; 2) neutrophil count ≤ 1.0 × 10^9 cells/L; 3) hospital acquisition; 4) detection of the episode in the intensive care unit; 5) male gender; 6) corticosteroid or cytotoxic therapy in the previous month; and 7) focus of infection. Foci with a high risk included the urinary tract with catheter or post-instrumentation, or the absence of an identifiable focus; those with a low risk were bone, joint, meninges, female genital tract and upper respiratory tract (Table 2).

The regression coefficients were used to compile a linear model in which one point was given for hospital acquisition, previous or current antibiotic treatment, detection of bacteremia in the intensive care unit and neutropenia. Half a point was added for male gender, corticosteroid or cytotoxic treatment, or the presence of a high-risk focus. For a low-risk focus, two points were subtracted (Table 2). The percentage of *P. aeruginosa* bacteremia in patients with an index score < 2 was 1.3% (37 of 2762 patients), 6.9% (74 of 1064 patients) with an index score of 2 or 3, and 19.3% (120 of 621 patients) with an index score > 3 (Table 3).

First validation set

During the study period, 2705 episodes of bacteremia were detected in 2627 patients at Beilinson Medical Center. *Pseudomonas aeruginosa* was isolated in 291 episodes (10.8%). The risk factors delineated in the St Thomas' data were significantly associated with *P. aeruginosa* bacteremia (Table 4).

When divided according to the index score, the percentage of *Pseudomonas* bacteremia in the first group

Table 3 Performance of the score index in the derivation and validation sets: Patients (n) with *Pseudomonas aeruginosa* bacteremia/total patients (n)

Index score	Derivation set	First validation set: Beilinson[a]	Second validation set: St Thomas', 1990-1993
< 2	37/2762 (1.3%)	89/1615 (5.5%)	26/1053 (2.5%)
2–3	74/1064 (6.9%)	143/815 (17.6%)	66/616 (10.7%)
> 3	120/621 (19.3%)	57/256 (22.3%)	48/234 (20.5%)
	p = 0.0001	p = 0.0001	p < 0.0001

a = Nineteen patients were excluded from this analysis because of missing values for one of the risk factors included in the index.

One point is given for previous or current antibiotic treatment, neutrophil count ≤1.0 × 10^9 cells/L, hospital acquisition and detection in the intensive care unit; half a point for male gender, high-risk focus of infection and corticosteroid or cytotoxic treatment; and −2 points for a low-risk focus.

(score < 2) was 5.5% compared with 17.6% in the second group (score of 2 to 3) and 22.3% in the third group (score > 3) ($p = 0.0001$; Table 3).

Of 291 episodes of pseudomonal bacteremia, 174 (59.8%) were given inappropriate empirical antibiotic treatment compared with 900 of 2414 episodes (37.3%) of bacteremia caused by other pathogens ($p = 0.0001$).

Second validation set

From 1990 to 1993, there were 1903 episodes of bacteremia detected at St Thomas' Hospital and *P. aeruginosa* was isolated on 140 occasions (7.4%) (Table 5). When divided according to the index score, the percentages of *Pseudomonas* bacteremia among the three groups were 2.5%, 10.7% and 20.5% (Table 3).

DISCUSSION

Seven risk factors were associated with *P. aeruginosa* bacteremia: neutropenia; cytotoxic or corticosteroid treatment; male gender; acquisition of infection in the hospital; detection of bacteremia in the intensive care unit; previous or current antibiotic treatment; and focus of infection. High rates of *P. aeruginosa* bacteremia were detected in patients who had evidence of urinary tract infection and a urinary catheter, or had undergone an invasive procedure of the urinary tract, and in those in whom no source of infection could be identified. A low risk of *P. aeruginosa* bacteremia was associated with a focus of infection in the bone, joint, meninges, female genital tract or upper respiratory tract.

Table 4 Validation set: Univariate comparisons of factors in patients with *Pseudomonas aeruginosa* bacteremia in Beilinson Medical Center

	Pseudomonas aeruginosa % ($n = 143$)	Other pathogens % ($n = 1274$)	p
Gender: Male	63.6	50.8	0.004
Adult intensive care unit	15.4	6.8	<0.0001
Neutrophil count $\leq 1 \times 10^9$ cells/L	15.4	7.8	0.002
Hospital-acquired	60.1	40.3	<0.0001
Previous/current antibiotic treatment	61.5	37.8	<0.0001
Focus of infection			
High risk	46.8	38.2	0.04
Low risk	0	2.1	0.08
Endotracheal intubation within previous month			
Present	15.4	7.6	0.001
Underlying disease			
Corticosteroid or imunosuppressive therapy	31.5	23.9	0.05

The magnitudes of these associations were similar in the two hospitals except for a significantly higher percentage of hospital-acquired pseudomonal bacteremia at St Thomas' Hospital. This is probably explained by the different definition of hospital-acquired bacteremia used in the two hospitals. Nevertheless, the discriminative power of the index was not affected by this difference. Most of these factors have also emerged in previous studies [5,7,8,13-19]. The present study is strengthened by the large number of patients surveyed and the use of regression analysis, which enabled identification of the factors that are the strongest predictors of *P. aeruginosa* bacteremia. In addition, the association of each factor with pseudomonal bacteremia was shown to be independent of the contribution of other factors and, finally, the magnitude of those associations was quantified. An index incorporating these risk factors allowed the allocation of patients to one of three groups with an increasing rate of *P. aeruginosa* bacteremia. At St Thomas' Hospital, these percentages were 1%, 7% and 19% and, at Beilinson Medical Center, 5%, 18% and 22%.

Both the risk factors and index retained their predictive power when tested in the Beilinson database, which suggests that the risk factors are not specific to one site (St Thomas' Hospital), but are universally associated with *P. aeruginosa* bacteremia. Furthermore, the robustness of the index score is demonstrated by the finding that its power was maintained over time although, from 1990 to 1993, neutropenia was no longer associated with pseudomonal infections. It is unclear whether this was a result of the occasional use

Table 5 Second validation set: Univariate comparisons of factors in patients with *Pseudomonas aeruginosa* bacteremia in St Thomas' Hospital from 1990 to 1993

	Pseudomonas aeruginosa % ($n = 140$)	Other pathogens % ($n = 1763$)	p
Gender: Male	61.4	53.1	0.05
Adult intensive care unit	42.9	18.8	<0.0001
Neutrophil count $\leq 1 \times 10^9$ cells/L	7.1	6.4	NS
Hospital-acquired	88.6	59.3	<0.0001
Previous/current antibiotic treatment	69.3	32.7	<0.0001
Focus of infection			
High risk	43.6	24.1	<0.0001
Low risk	0.7	6.8	0.005
Underlying disease			
Corticosteroid or imunosuppressive therapy	14.3	9.2	0.05

of 4-quinolones at St Thomas' Hospital as prophylaxis against infection or whether neutropenia induced by cytotoxic therapy was of a shorter duration than in previous years. The other associations remained so powerful that the performance of the index was not affected. Nevertheless, this change emphasizes the need to monitor the predictive power of each component of a predictive index over time.

The overall percentage of bacteremic infections caused by *P. aeruginosa* is higher at Beilinson Medical Center and also within each group defined by the index, although the gradation between groups was maintained. The actual percentage of *Pseudomonas* bacteremia in each group is dictated by the overall frequency of *P. aeruginosa* bacteremia (the 'pretest probability'), which must be borne in mind when the index is applied in clinical practice. In any case, a patient suspected of bacteremia and with an index score < 2 (first group) should probably not be given empirical antipseudomonal treatment whereas the chance of a pseudomonal infection in a patient with an index score > 3 (third group) is substantial.

The 'denominator set' in this study was a group of patients with proven bacteremia whereas the true denominator group in clinical practice should be patients suspected of bacteremia. However, in previous studies, we and others have shown that the use of simple clinical and laboratory data, which are known within hours of detection of an infectious episode, can define groups of patients at high risk for bacteremia [20-23]. In such patients, the use of the present index will probably improve empirical treatment of *P. aeruginosa* bacteremia.

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References

1. Weinstein MP, Reller LB, Murphy JR, Lichtenstein KA. The clinical significance of positive blood cultures: A comprehensive analysis of 500 episodes of bacteremia and fungemia in adults. I. Laboratory and epidemiological observations. Rev Infect Dis 1983; 5: 35-53.
2. Rayner BL, Willcox PA. Community-acquired bacteraemia: A prospective survey of 239 cases. Quart J Med 1988; 69: 907-19.
3. Gattel JM, Trilla A, Latorre X, et al. Nosocomial bacteremia in a large Spanish teaching hospital: Analysis of factors influencing prognosis. Rev Infect Dis 1988; 10: 203-10.
4. Eykyn SJ, Gransden WR, Phillips I. The causative organisms of septicaemia and their epidemiology. J Antimicrob Chemother 1990; 25(suppl C): 41-58.
5. Leibovici L, Konisberger H, Pitlik SD, Samra Z, Drucker M. Bacteremia and fungemia of unknown origin in adults. Clin Infect Dis 1992; 14: 436-43.
6. Miller PJ, Wenzel RP. Etiologic organisms as independent predictors of death and morbidity associated with bloodstream infections. J Infect Dis 1987; 156: 471-7.
7. Bodey GP, Jadeja L, Elting L. *Pseudomonas* bacteremia: Retrospective analysis of 410 episodes. Arch Intern Med 1985; 145: 1621-9.
8. Bisbe J, Gatell JM, Puig J, et al. *Pseudomonas aeruginosa* bacteremia: Univariate and multivariate analysis of factors influencing the prognosis in 133 episodes. Rev Infect Dis 1988; 10: 629-35.
9. Hilf M, Yu VL, Sharp J, Zuravleff JJ, Korvick JA, Muder RR. Antibiotic therapy for *Pseudomonas aeruginosa* bacteremia: Outcome correlations in a prospective study of 200 patients. Am J Med 1989; 87: 540-6.
10. Leibovici L, Konisberger H, Pitlik SD, Samra Z, Drucker M. Patients at risk for inappropriate antibiotic treatment of bacteremia. J Intern Med 1992; 231: 371-4.
11. Gransden WR, Eykyn SJ, Phillips I. The computerized documentation of septicaemia. J Antimicrob Chemother 1990; 25(suppl C): 31-9.
12. Harrell FE. The LOGIST procedure. In: SAS Institute Inc. SUGI supplemental library user's guide, version 5. Cary, NC, USA. SAS Institute 1986; 269-93.
13. Griffith SJ, Nathan C, Selander RK, et al. The epidemiology of *Pseudomonas aeruginosa* in oncology patients in a general hospital. J Infect Dis 1989; 160: 1030-6.
14. Ehni WR, Reller LB, Ellison RT. Bacteremia in granulocytopenic patients in a tertiary-care general hospital. Rev Infect Dis 1991; 13: 613-9.
15. Gallagher PG, Watanukunakorn C. *Pseudomonas* bacteremia in a community teaching hospital, 1980-1984. Rev Infect Dis 1989; 11: 846-52.
16. Leibovici L, Konisberger H, Pitlik SD, Samra Z, Drucker M. Predictive index for optimizing empiric treatment of gram-negative bacteremia. J Infect Dis 1991; 163: 193-6.
17. Gransden WR, Phillips I. Predictive index for optimizing empiric treatment of gram-negative bacteremia. J Infect Dis 1991; 164: 211-2.
18. McKendrick MW, Geddes AM. *Pseudomonas* septicaemia in a general hospital – seven years experience. Quart J Med 1981; 50: 331-44.
19. Vazquez F, Mendoza MC, Villar MH, Vindel A, Mendez FJ. Characteristics of *Pseudomonas aeruginosa* strains causing septicemia in a Spanish hospital 1981-1990. Eur J Clin Microbiol Infect Dis 1992; 11: 698-703.
20. Mellors JW, Horwitz RI, Horwitz SM. A simple index to identify occult bacterial infection in adults with acute unexplained fever. Arch Intern Med 1987; 147: 666-71.
21. Leibovici L, Cohen O, Wysenbeek AJ. Occult bacterial infections in adults with unexplained fever: Validation of a diagnostic index. Arch Intern Med 1990; 150: 1270-2.
22. Bates DW, Cook EF, Goldman L, Lee TN. Predicting bacteremia in hospitalized patients. A prospectively validated mode. Ann Intern Med 1990; 113: 495-500.
23. Leibovici L, Greenshtain S, Cohen O, Mor F, Wysenbeek AJ. Bacteremia in febrile patients: A clinical model for diagnosis. Arch Intern Med 1991; 151: 1801-6.